PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

Vol. 22, No. 6 June 2008

NEONATAL DISORDERS

PATTERNS OF BRAIN INJURY IN HYPOXIC ENCEPHALOPATHY

Researchers at Imperial College, Hammersmith, London, UK, studied patterns of brain injury in term neonates with hypoxic encephalopathy, risk factors, and the correlation between neuroimaging abnormalities and developmental outcomes at a minimum of 12 months. Prenatal and perinatal data were compared with those for normal term low-risk infants. Among 500 term neonates with encephalopathy studied with MRI between 1992 and 2005, 48 had preceding acute hypoxia. MRI scans were obtained at a median age of 10 days, none > 6 weeks. Five patterns of brain injury were identified: 1) basal ganglia and thalami lesions with severe white matter damage in 6 (14%); 2) basal ganglia and thalami lesions with mild or moderate white matter changes in 24 (56%); 3) isolated thalamic injury in 2 (5%); 4) moderate white matter damage only in 1 (2%); and 5) mild white matter changes or normal findings in 10 (23%). Infants with patterns 1) and 2) showed internal capsule abnormalities in 93%, and 86% died or developed cerebral palsy. Infants with patterns 3) and 4) had developmental delay and diplegic cerebral palsy, respectively. Outcome was normal in infants with pattern 5). Risk factors included African ethnicity, and maternal pluriparity or hypertension. Birth complications included uterine rupture following previous cesarean section in 8 of 11 cases, and cord prolapse accompanying undiagnosed breech presentation in 4 of 9 cases. Basal ganglia and thalami lesions in the MRI of term infants are indicative of neonatal hypoxic-ischemic encephalopathy. Patterns of central gray matter and secondary white matter injury are associated with poor outcome. Delivery should be expedited in infants at risk of sentinel events (eg. umbilical cord prolapse, placental abruption). (Okereafor A, Allsop J, Counsell SJ, et al. Patterns of brain injury in neonates exposed to perinatal sentinel events. **Pediatrics** May 2008;121:906-914). (Respond: Frances M Cowan MRCPCH, PhD, Department of Paediatrics and Neonatal Medicine, 5th Floor, Ham House, Hammersmith Hospital, Du Cane Rd, London W12 OHS, UK.)

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COMMENT. Abnormalities in the basal ganglia associated with perinatal asphyxia were described in clinical and neuropathological studies in the mid-20th century and earlier, especially in relation to cerebral palsy. (Norman RM. In: **Greenfield's Neuropathology**. Baltimore, Williams and Wilkins, 1963; pp. 390-397; Christensen E, Melchior J. Cerebral palsy – A clinical and neuropathological study. **Clin Dev Med** 1967;25:1; Ingram TTS. **Paediatric Aspects of Cerebral Palsy**. Edinburgh, E & S Livingstone, 1964). *Status marmoratus* (etat marbre), marbling of the basal ganglia is a well-recognized pathological finding in children with athetoid CP. Regarded initially as a prenatal developmental anomaly (Vogt C, Vogt O. **J Psychol Neurol** 1919;24:1, cited in Ingram 1964) etat marbre is now considered a sequel to perinatal birth anoxia, and associated with a history of asphyxia or trauma or, sometimes, kernicterus or status epilepticus. The thalami and other brain regions may also be affected. Characteristically, shrinkage of the basal ganglia is accompanied by coarse networks of myelinated nerve fibers, termed dysmyelination or hypermyelination. Stained by Weigert's method, the myelin marbled appearance is revealed as alternating light and dark areas in the putamen and caudate nuclei. Some well known pediatric neurologists have contributed to our understanding of the syndrome of status matmoratus and CP, including Crothers B. **Amer J Dis Child** 1921;22:145; and Ford FR. **Diseases of the Nervous System in Infancy, Childhood and Adolescence**. 4th ed. Springfield, IL. Charles C Thomas, 1960.

In the Hammersmith study report, status marmoratus is not mentioned as a possible pathology involving the basal ganglia of patients who developed athetoid cerebral palsy or in the 8 infants who died. Presumably, autopsies were not obtained. MRI descriptions of the basal ganglia abnormalities in the neonatal period showed swelling and homogeneous appearance, not shrunken and marbled. Status marmoratus may develop as a late finding in older CP patients. My colleague, Dr Mark Wainwright provided the following references to the MRI in patients with cerebral palsy: Mizuguchi M and Takashima S (**Neuropathology** 2002;22:85-89) report that radiological techniques are unable to visualize or identify pathological changes of status marmoratus; and reporting results of the European CP Study, Bax M and associates (**JAMA** 2006;296:1602-1608) found basal ganglia abnormalities in 12.8%, described as reduction in volume and increased signal in a child aged 18 months with dyskinetic CP. MRI obtained at 18 months of age or later was normal in 11% of children with CP.

PRE-TERM AND PERINATAL PREDICTORS OF NEONATAL HIPPOCAMPAL VOLUMES

Hippocampal volumes of 184 preterm (PT) and 32 full-term (FT) infants were measured by segmental MRI at term equivalent age in an investigation of correlations of preterm hippocampal volume, perinatal risk factors, and neurodevelopmental outcome, at University of Melbourne, Victoria, and other centers in Australia; St Louis and Boston, USA; and Geneva, Switzerland. No significant differences between PT and FT infant hippocampal volumes were detected, after controlling for head size. Factors associated with significantly smaller hippocampal volumes included white matter injury, exposure to postnatal steroids, and treatment with indomethacin. Smaller PT hippocampal volumes correlated with impaired cognitive and psychomotor development measured by the Bayley Scales at 2 years of age,

after correcting for head size and sex. (Thompson DK, Wood SJ, Doyle LW, et al. Neonate hippocampal volumes: prematurity, perinatal predictors, and 2-year outcome. **Ann Neurol** May 2008;63:642-651). (Resapond: Deanne K Thompson, BSc(Hons), Howard Florey Institute, Level 2, Alan Gilbert Building, 161 Barry Street, Carlton South, VIC 3053, Australia).

COMMENT. The hippocampus, part of the limbic lobe, originally linked mainly with olfactory function, is now considered important in memory, spatial function, and cognition. Hippocampal volume reduction reported in children with chromosome 22q11.2 deletion syndrome is correlated with severity of cognitive impairment. (Deboer T et al. **Behav Brain Funct** 2007;3:54). Severe memory impairment is reported in a 5-year-old child with marked hippocampal atrophy after prolonged status epilepticus. (Jambaque I et al. **Dev Med Child Neurol** 2007;49:398-399). The authors of the above report in infants recommend further MRI studies in older children to determine the role of the hippocampus in the high rate of cognitive impairment in preterm infants tested at a later age. They advocate interventions to decrease white matter damage and overuse of postnatal steroids and indomethacin in preterm infants, factors linked to smaller hippocampal volume.

VERY PRETERM BIRTH, CEREBELLAR DEVELOPMENT AND NEUROPSYCHOLOGICAL OUTCOME IN ADOLESCENCE

Cerebellar volumes were measured on structural MRI at adolescence and adulthood in 65 preterm individuals (born before 33 weeks' gestation), and a term-born comparison group, in a study at King's College, Great Ormond Street Hospital, and University College, London; and Seoul National University College of Medicine, Korea. Cerebellar volumes in late adolescence and adulthood (mean age 18.6;SD=1.02) were 3.11% and significantly smaller than measurements during early adolescence (mean age 15 years;SD=1.43) in the preterm group (P=0.000), whereas cerebellar volumes increased 0.44%, but did not change significantly with age in the control group (P=0.612). The changes in cerebellar volume correlated with tests of behavior and cognitive function. High General Health Questionnaire (GHQ)-12 scores, a self-reporting wellbeing test (eg feeling worthless, poor concentration), indicative of increased risk of mental health problems, correlated with reduction in cerebellar volume during late adolescence and young adulthood. Cerebellar volume correlated positively with full scale, verbal and performance IQ in early adolescence in the very preterm group but not the term-born group. Correlations with IQ were not maintained after controlling for white matter volume. (Parker J, Mitchell A, Kalpakidou A, et al. Cerebellar growth and behavioural & neuropsychological outcome in preterm adolescents. **Brain** May 2008;131:1344-1351). (Respond: Matthew Allin, Kung's College London, Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, London, UK. E-mail: matthew.allin@iop.kcl.ac.uk)

COMMENT. A decrease in cerebellar volume occurring between mean age 15 years and 18.6 years in very preterm individuals is correlated with impaired feelings of wellbeing, but a correlation with IQ deficits is not significant when controlled for white matter volume. These findings corroborate previous reports of cerebellar involvement in cognitive and neurobehavioral disorders. (Murakami JW et al. **Arch Neurol** 1989;46:689-694).

IDIOPATHIC INFANTILE NYSTAGMUS, WITH AND WITHOUT *FRMD7* GENE MUTATIONS

Clinical features and eye movement recordings of 90 subjects with mutations in the gene (*FRMD7* group) were compared to 48 without mutations (non-*FRMD7* group) but with clinical idiopathic infantile nystagmus (IIN), in a study at University of Leicester, Leicester Royal Infirmary, Leeds General Infirmary, Royal Preston Hospital, Addenbrooks Hospital, Cambridge, UK; Wills Eye Hospital, Philadelphia, USA; and Medical University Graz, Austria. Visual acuity and binocular vision were generally normal in both groups. Prevalence of strabismus was similar and occurred in 7.8% of mutation and 10% of non-FRMD7 patients. Anomalous head posture was significantly more frequent in the non-FRMD7 group ($P<0.0001$); moderate (5-15 degrees) in 24% and severe (>15) in 27% vs 17% only moderately affected in the FRMD7 group. Amplitude of nystagmus was lower at primary position in the FRMD7 group ($P<0.0001$) compared to non-FRMD7 group ($P=0.83$). Pendular nystagmus was more frequent in the FRMD7 group ($P=0.003$). Obligate female carriers of an FRMD7 mutation were clinically affected in 53%. Visual acuity of affected females was better than affected males ($P=0.014$). FRMD7 is a major cause of X-linked IIN. The findings are helpful in genetic counselling of patients with idiopathic infantile nystagmus. (Thomas S, Proudlock FA, Sarvananthan N, et al. Phenotypical characteristics of idiopathic infantile nystagmus with and without mutations in FRMD7. **Brain** May 2008;131:1259-1267). (Respond: Prof Irene Gottlob, Ophthalmology Group, University of Leicester, Faculty of Medicine & Biological Sciences, Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester, LE2 7LX, UK. E-mail: ig15@le.ac.uk).

COMMENT. Idiopathic infantile nystagmus is noted in the first months of life, and diagnosis is dependent on the absence of albinism and congenital night blindness or achromatopsia. Prevalence of nystagmus is estimated at 2.4/1000 (Sarvananthan N et al. **Invest Ophthalmol Vis Sci** 2006;47:E-Abstract 2656). Inheritance is X-linked most commonly, and the present authors report multiple mutations in FRMD7 gene localized to chromosome X (NYS1). In addition, autosomal dominant inheritance is described, localized to chromosome 6, as well as autosomal recessive inheritance. In patients with idiopathic infantile nystagmus, clinical characteristics of those with FRMD7 mutation are similar to a non-FRMD7 mutation group, except abnormal head posture is significantly less frequent and amplitude of nystagmus in the primary position is lower in those with mutations. Most patients with IIN have good visual acuity and stereopsis and strabismus is infrequent, in both those with and without mutations. Mutations in FRMD7 are the major cause of inherited IIN. Cerebellar dysfunction is the most likely cause of nystagmus related to the FRMD7 gene in IIN. (Glasauer S. **Ann NY Acad Sci** 2003;1004:206-219).

MANAGEMENT OF NEONATAL SEIZURES

The generally accepted clinical approaches to neonatal seizures were determined by questionnaires completed by pediatric neurologists and neonatologists representing all the pediatric neurology units and all departments of neonatology in Isrrael, and were evaluated at

Tel Aviv Sourasky Medical Center. Responding 36/55 (65%) neurologists and 66/112 (59%) neonatologists chose similar antiepileptic drugs as first line (phenobarbital), second line (phenytoin), and third line (benzodiazepines) treatments. Treatment duration favored by both specialties varied widely from 1-52 weeks, neurologists tending to recommend longer treatment for seizures secondary to asphyxia or hemorrhage. For intractable neonatal seizures, neurologists favored valproic acid and topiramate, and neonatologists recommended lidocaine and benzodiazepines (P=0.0023). Continuous EEG monitoring after asphyxia was used by 70.5% of neonatologists contrasting with only 40% of neurologists (P=0.013). Specialties differed concerning the harmfulness of neonatal seizures: 76% neurologists cf 55% neonatologists answered "Yes" to "Could neonatal seizures harm the brain?" (P=0.065); 12% neurologists cf 34% neonatologists answered "Don't know." "Could electrographic seizures harm the brain?;" 43% neurologists and 47% neonatologists answered "Don't know." "Would you treat electrographic seizures?," 40% neurologists and 38% neonatologists answered "Yes." Controlled clinical trials to establish evidence-based guidelines for the management of neonatal seizures are indicated. (Bassan H, Bental Y, Shany E et al. Neonatal seizures: dilemmas in workup and management. **Pediatr Neurol** June 2008;38:415-421). (Dr Haim Bassan, Neonatal Neurology Service, Dana Children's Hospital, Tel Aviv Sourasky Medical Center, 6 Weizmann Dr, Tel Aviv 64239, Israel. E-mail: bassan@post.tau.ac.il).

COMMENT. Israeli neurologists and neonatologists agree on initial management, but differ on treatment of intractable neonatal seizures, the harmfulness of neonatal seizures on developing brain, and need to monitor subclinical seizure activity. "Don't know" was a frequent answer by both specialties to questions regarding harmfulness of electrographic seizures and the need to treat them. Controversies in the literature need further research and answers.

Lamotrigine for partial seizures in patients aged 1 to 24 months was well tolerated and may be effective as adjunctive therapy, as shown by a randomized, double-blind, placebo-controlled study in 19 patients at Vanderbilt University, Nashville, TN (Pina-Garza, Levisohn P, Gucuyener K, et al. **Neurology** May 27, 2008;70:2099-2108). Rash occurred in 15% during the open label phase; none was Stevens-Johnson syndrome or toxic epidermal necrolysis. Children <2 years of age are considered therapeutic orphans since antiepileptic drug trials are hampered by multiple restrictions. This study demonstrates that drug trials at this age can be completed. (Goodkin HP, Buck ML. Editorial. **Neurology** 2008;70:2093-2094).

INFECTIOUS DISORDERS

MATERNAL INFECTION AND RISK OF EPILEPSY IN CHILDHOOD

The association between prenatal exposure to maternal specific infections during pregnancy and the subsequent risk of epilepsy in childhood was estimated in a prospective population-based birth cohort in Denmark followed for 8 years at University of Aarhus, Denmark. Of 90619 singletons, 646 children were identified with a diagnosis of epilepsy in the follow-up period. Children exposed to maternal cystitis in each trimester, pyelonephritis,

diarrhea lasting >4 days in the first 2 trimesters, coughs, and/or vaginal yeast infection in prenatal life had an increased risk of epilepsy. Cough lasting >1 week was a risk factor only in the first year of life, and vaginal yeast infection only in children born preterm. Genital herpes, venereal warts, and herpes labialis were not risk factors. These associations were not changed in children with cerebral palsy (0.2%), congenital malformation (7.2%), or low Apgar (<7) at 5 minutes (1.8%). (Sun Y, Vestergaard M, Christensen J, Nahmias AJ, Olsen J. Prenatal exposure to maternal infections and epilepsy in childhood: a population-based cohort study. **Pediatrics** May 2008;121:e1100-e1107). (Respond: Yuelian Sun MD, Department of Epidemiology, University of Aarhus, Vennelyst Blvd 6, Aarhus, 8000 C, Denmark. E-mail: ys@soci.au.dk).

COMMENT. Some maternal infections are associated with an increased risk of epilepsy during childhood. The mechanisms underlying the associations are unknown, but fever and cytokines are possible factors. (Adinolfi M. **Dev Med Child Neurol** 1993;35:549-553; Dammann O, Leviton A. **Pediatr Res** 1997;42:1-8).

CONGENITAL CYTOMEGALOVIRUS INFECTION AND RISK OF EPILEPSY

The clinical, laboratory and neuroradiological findings in 19 children with congenital cytomegalovirus (CMV) infection were retrospectively reviewed for features of epilepsy in 7 (37%), in a study at Osaka Medical Center, Japan. Partial seizures occurred in 5 at a mean age of 20 months (range 2-37 months), West syndrome occurred in 3 patients. Seizures were uncontrolled at time of last follow-up (mean 96 months) in 6 patients. Neonatal clinical features (gestational age, gender, birth asphxia, microcephaly, chorioretinitis, neonatal seizure) were not predictive of development of epilepsy with CMV, whereas imaging abnormalities (ventricular dilatation and migration disorder) were risk factors. (Suzuki Y, Toribe Y, Mogami Y, Yanagihara K, Nishikawa M. Epilepsy in patients with congenital cytomegalovirus infection. **Brain & Dev** June 2008;30:420-424). (Respond: Dr Yasuhiro Suzuki. E-mail: yasuzuki@mch.pref.osaka.jp).

COMMENT. Neuroradiographic findings, rather than clinical symptoms at birth, are most predictive of development of epilepsy in children with CMV infection. West syndrome in 43% of 7 patients in this series is a lower prevalence for this seizure type than expected.

HERPES SIMPLEX VIRUS TYPE 2 NEUROLOGIC COMPLICATIONS

The neurologic complications of HSV-2 infection are reviewed by researchers at University of Kentucky College of Medicine, Lexington. HSV-2-associated neurologic disease results from primary infection or reactivation of latent HSV-2. Primary infection occurs in neonates but is usually delayed until adolescence and adulthood, following sexual activity. HSV-2 latency and reactivation is centered in sacral ganglia, but may also be widespread in the CNS. Approximately 90% of infections are unrecognized. Neurological complications of HSV-2 infection involve any part of the neuraxis. Encephalitis (HSE) is the most frequent manifestation of HSV-2 in neonates, and onset is heralded by focal or generalized seizures. CSF shows a lymphocytic pleocytosis, increased protein, and PCR

positive for HSV-2. Compared to HSV-1 infection, HSV-2 encephalitis has a higher frequency of seizures, greater pleocytosis and protein level in CSF, and more severe structural brain damage on imaging. Other neurological complications of HSV-2 infection occur mainly in adults and include acute aseptic meningitis, recurrent aseptic meningitis (sometimes called Mollaret meningitis), ascending myelitis, lumbosacral radiculopathy, cranial neuropathy (Bell palsy), and acute retinal necrosis. HSV-2 CNS complications appear early in the course of HIV/AIDS. Diagnosis of HSV infection of the nervous system is made by PCR assays of CSF. Viral culture and serological assays for HSV antibodies may also be useful. Acyclovir is standard therapy. (Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. **Arch Neurol** May 2008;65:596-600). (Respond: Joseph R Berger MD, Department of Neurology, University of Kentucky College of Medicine, Kentucky Clinic Room L-445, 740 S Limestone St, Lexington, KY 40536. E-Mail: jrbneuro@uky.edu).

COMMENT. American Academy of Pediatrics Red Book (27th ed, 2006) finds that one third of cases of HSV infection in the neonate involve the CNS. CNS disease usually manifests between the second and third weeks of life. HSV-2 is the most common cause of disease in neonates, and accounts for 75% of cases.

SEIZURE DISORDERS

MRI ABNORMALITIES AND FIRST FEBRILE SEIZURES

The frequency of MRI-detected brain abnormalities with first febrile seizures (FS) and their association with FS type and with specific features of complex FS were determined in a prospective study at the Pediatric Emergency Department of New York-Presbyterian Children's Hospital, Columbia University, New York. MRI performed within 1 week of the first FS showed abnormalities in 12.6% of 159 children affected. The number and ratio of simple to complex FS was 105:54 or 2:1. Imaging abnormalities occurred in 11.4% with simple FS and 14.8% of complex FS (n.s.). Of 54 complex FS cases, those with both focal and prolonged FS (N=14, 26%) were more likely to have MRI abnormalities than simple FS cases. These included focal cortical dysplasia and gray matter heterotopia (known to be associated with seizures) and subcortical focal hyperintensities (=/> 5 mm) and delayed myelination (not typically associated with seizures). Focal hyperintensities, the most common abnormality with first FS, were more frequent in children with complex (N=7, 13%) compared to simple FS (N=1, 0.9%, p=0.001). In comparison, the NIH Study of Normal Brain Development found no brain abnormalities on baseline MRI scans. Brain abnormalities may be associated with a lower seizure threshold in febrile children, predisposing to the development of FS. The findings did not affect our clinical management of FS, and MRI is unnecessary in FS, without some other neurological indication. (Hesdorffer DC, Chan S, Tian H, et al. Are MRI-detected brain abnormalities associated with febrile seizure type? **Epilepsia** May 2008;49:765-771). (Respond: Dale C Hesdorffer PhD, GH Sergievsky Center, Columbia University, P & S Unit 16, 630 West 168th Street, New York, NY 10032. E-mail: dch5@columbia.edu).

COMMENT. AAP Practice Parameters on the evaluation and treatment of first simple febrile seizures (1996) advise against investigation with MRI, CT, or EEG, MRI abnormalities are reported in patients with febrile status epilepticus (Scott RC et al, 2003), but studies following first FS are understandably lacking, having regard to the hazards of heavy sedation in infants. Most neurologists consider MRI and EEG are indicated in children with recurrence of complex FS, prolonged impairment of consciousness following a seizure, or abnormal neurological signs. In the above prospective study of first FS, the incidence of abnormal MRIs in simple FS is unexpected, given the presumed benign nature of the FS. Although the finding did not change the clinical management of FS in this institution, the brain lesions are important in our understanding of the mechanism of FS. Authorities are divided regarding inclusion of children with a history of birth injury as FS, and some have grouped such patients as having epilepsy (Livingston (1954) and Friderichsen and Melchior (1954)). In unselected series of patients, however, evidence suggests that the threshold to FS may be lowered by both inherited and acquired factors. In addition to the essential role of fever, birth injury or anoxia and structural cerebral pathology may be factors in etiology and should not negate the diagnosis of FS. (Millichap JG et al, 1960). The necessity to guard against selection bias by such arbitrary exclusions is stressed by Baumann RJ and others (in **Febrile Seizures**. Eds. Nelson KB, Ellenberg JH. New York, Raven Press, 1981).

In the Columbia University study, the proportion of complex FS (both focal and prolonged) is high (25%), accounting for the higher frequency of MRI abnormalities among this group. An 11% incidence of MRI abnormalities in patients with simple FS is a novel finding, however, and suggests that febrile seizures are less benign than generally assumed. Without some other neurological indication, MRI is not recommended in children with FS. In support of this conclusion, a recent report of the management of FS in an unselected series of 100 patients found no structural brain abnormality in CT performed in 18% and MRI performed in 4% of FS patients. Head CT was obtained in 6% (4/77) of simple FS cases (1 had mastoiditis) and 61% (14/23) of complex cases. In keeping with AAP guidelines, no simple FS patients were examined with MRI; 17% of complex FS received MRI and all were normal (Millichap JJ. Febrile seizure management in hospital practice compared to recommended guidelines. **AAN 60th Annual Meeting**, Chicago, 2008:A131, Abstract PO3.006). The frequency of negative CT scans in FS studies is noteworthy, and more specific indications for neuroimaging in children with complex FS should be determined.

ATTENTION DEFICIT DISORDERS

ST JOHN'S WORT COMPLEMENTARY THERAPY FOR ADHD

A randomized, double-blind, placebo-controlled trial of hypericum perforatum (St John's Wort) in the treatment of attention-deficit/hyperactivity disorder (ADHD) was conducted in 54 children aged 6 to 17 years at Bastyr University, Kenmore, WA. No significant differences were found in: (1) the change in ADHD Rating Scale-4 scores from baseline to week 8 between the treatment and placebo groups; (2) the percentage of children showing improvement on the Clinical Global Impression Improvement Scale; or (3) the number experiencing adverse events. (Weber W, Stoep AV, McCarty RL, et al. **JAMA** June 11, 2008;299:2633-2641). (Respond: Wendy Weber ND, PhD, MPH, 14500 Juanita Dr NE, Kenmore, WA 98028. E-mail: wendyw@bastyr.edu).